THE ACUTE TOXICITY OF BRIEF EXPOSURES TO HYDROGEN FLUORIDE, HYDROGEN CHLORIDE, NITROGEN DIOXIDE, AND HYDROGEN CYANIDE SINGLY AND IN COMBINATION WITH CARBON MONOXIDE

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13. ABSTRACT

This report was presented at the Proceedings of the 2nd Annual Conference on Environmental Toxicology, sponsored by the SysteMed Corporation and held in Fairborn, Ohio on 31 August, 1 and 2 September 1971. Major technical areas discussed included toxicological evaluation of volatile halogenated compounds, protection of the public against air pollution and toxicological problems with aircraft, missiles, and space vehicles.

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THE ACUTE TOXICITY OF BRIEF EXPOSURES TO HYDROGEN FLUORIDE, HYDROGEN CHLORIDE, NITROGEN DIOXIDE, AND HYDROGEN CYANIDE SINGLY AND IN COMBINATION WITH CARBON MONOXIDE

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INTRODUCTION

Many of the common plastic and rubber formulations in widespread use as aircraft cabin materials represent potential hazards in the event of fire aboard an aircraft. For example, polyurethane foams contain diisocyanate, fluorinated and chlorinated hydrocarbons, in addition to various aliphatic amines (Gleason et al., 1969). When subjected to the high temperatures of combustion, the pyro-decomposition products formed would include hydrogen chloride (HCl), hydrogen fluoride (HF), hydrogen cyanide (HCN), and nitrogen dioxide (NO_2) gases. Because of the inadequacy of available information regarding toxicity of these gases under very brief exposure conditions, animal experiments were conducted using these compounds, both singly and in combination with carbon monoxide (CO), to determine five-minute LC_{50} values. Joint exposures with CO were performed since in all probability incomplete combustion during an aircraft fire would produce measurable concentrations of atmospheric CO. We wanted to see just what, if any, effect the CO would have on the toxicity of these several compounds. Since both civilian and military aircraft fires produce the same variety of pyro-decomposition products, this research was co-sponsored by the Federal Aviation Agency and the United States Air Force.

MATERIALS AND METHODS

Exposure groups for five-minute LC_{50} determinations of the four test materials were comprised of male Wistar rats, 10 per group, ranging in weight from 250-275

Begin → 279

grams, and male ICR mice, 15 per group, ranging from 30-35 grams. Exposed animals were observed for seven days postexposure to allow sufficient time for any delayed deaths resulting from pulmonary edema. LC_{50} values were calculated by the method of Litchfield and Wilcoxon (1949) using computer program techniques. This method results in a slope calculated by the method of least squares, providing the lowest Chi square values possible.

The tests consisted of dynamic five-minute exposures using a Rochester Chamber (Leach et al., 1959), modified with sliding cage drawers to facilitate rapid insertion and withdrawal of the test animals. This modification is shown in figure 1. The chamber concentration was equilibrated at the desired level and the caged animals were inserted through the opening, thus commencing the exposure.

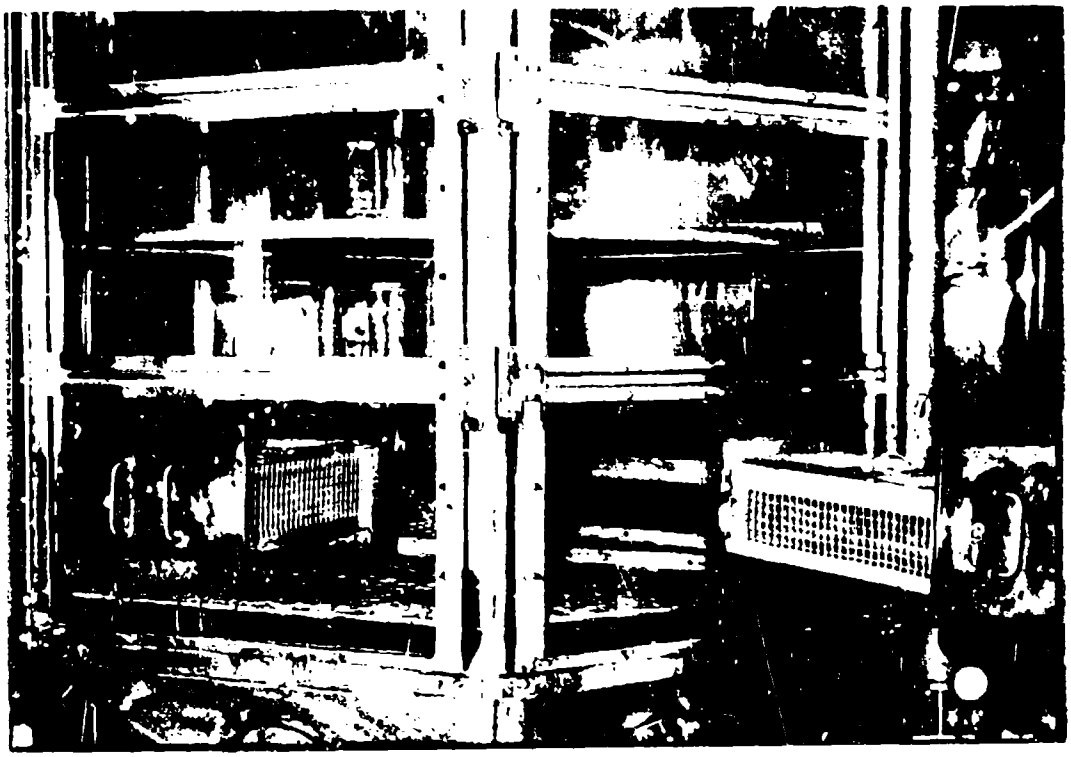


Figure 1. ROCHESTER CHAMBER MODIFIED TO ACCEPT SLIDING CAGE DRAWERS

Generation of HCl, HF, and CO consisted of metering the desired quantities from a standard gas cylinder into the exposure chamber. Hydrocyanic acid was metered as a liquid into a glass evaporator. The vapors were then transferred to the exposure chamber. The NO_2 gas cylinder was immersed in a constant temperature water bath in order to prevent condensation in the generation system. Vapors from this cylinder were then metered as desired to the exposure chamber.

Continuous analysis was provided for each of the compounds tested. Chamber concentrations of HCl, HF, and HCN were absorbed in aqueous reagent solution then measured using Coleman specific ion electrodes. Calibration curves were prepared by sampling known concentrations of the specific ion made from the primary standards NaCl, NaF, or NaCN. Chamber concentrations of NO_2 were absorbed in Saltzman Reagent (Saltzman, 1960) and analyzed spectrophotometrically using a Technicon AutoAnalyzer. NO_2 calibration curves were prepared by both vapor bag and permeation tube standardization (O'Keeffe and Ortman, 1966).

Determination of CO Concentration

A preliminary series of five-minute exposures was conducted to determine the atmospheric concentration of CO required to produce 25% carboxyhemoglobin (COHb) blood levels in rats and mice. This COHb concentration was chosen because, although not lethal in man, it is sufficient to produce minor CNS effects (Swinyard, 1970). Rats and mice were exposed to various CO concentrations for five minutes, at which time blood samples were drawn immediately. These samples were then analyzed for COHb content by a gas chromatographic technique which measures the CO moiety of COHb (Goldbaum et al., 1963). Our analyses indicated that 2100 ppm CO was sufficient to produce 25% COHb in rats exposed for five minutes, while 1500 ppm CO produced the same effects in mice. These respective CO concentrations were then used in combination with the test materials (HCl, HF, NO_2, or HCN) for the series of joint action experiments.

HYDROGEN FLUORIDE AND HYDROGEN CHLORIDE RESULTS

Symptomatology

There were a number of toxic signs noted both during and after exposure to HF and HCl vapors. Included among these were brittling and discoloration of fur, respiratory distress, corneal opacities, rhinorrhitis, and severe burns on exposed surface areas of the skin. Delayed deaths were normally seen with both of these compounds in concentrations below the LC_{50} level Peak mortality usually occurred by 24 hours postexposure, although some deaths were noted three to four days later. The time-to-death pattern did not appear to be influenced by the presence of CO for either the HF or the HCl exposures.

Mortality Response

Figure 2 shows the LC_{50} slopes for five-minute exposures of rats to HF, both singly and in combination with the predetermined 2100 ppm CO. The five-minute LC_{50} for HF alone was determined to be 18, 200 ppm, while for the HF-CO combination this value was 18, 208 ppm. There is no significant difference between these two values.

Figure 3 shows the LC_{50} slopes for five-minute exposures of mice to HF vapors singly and in combination with CO. Here again, there is no significant difference between the two LC_{50} values. For mice, the five-minute HF LC_{50} is 6, 247 ppm in contrast to the 6, 670 ppm LC_{50} for the HF-CO combination.

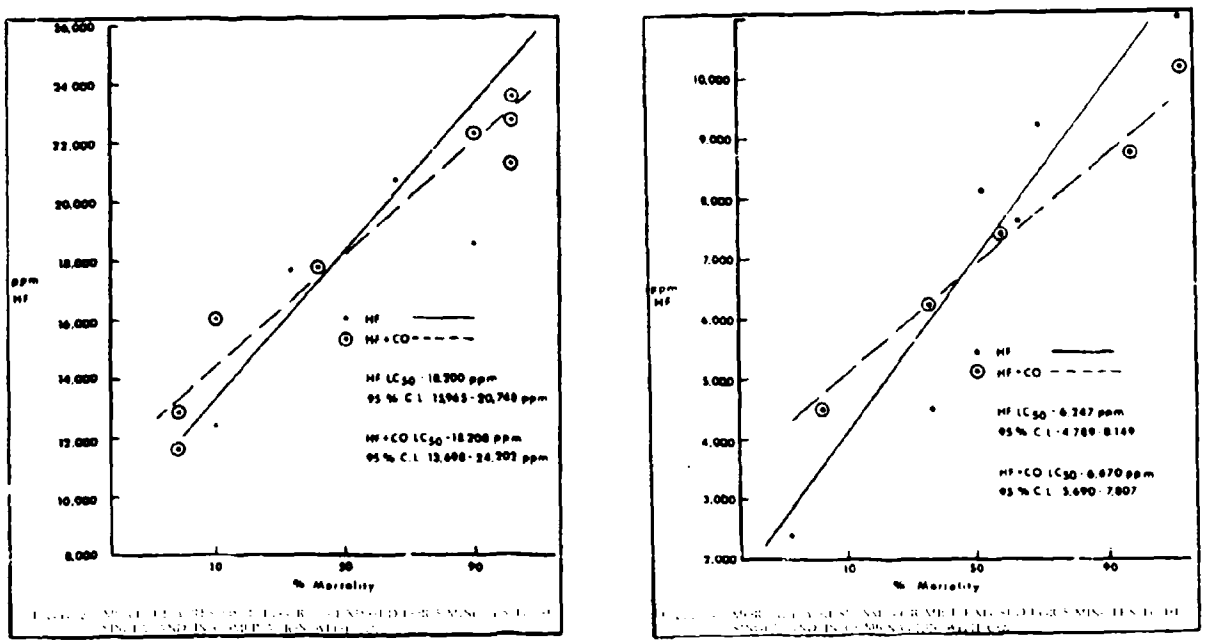
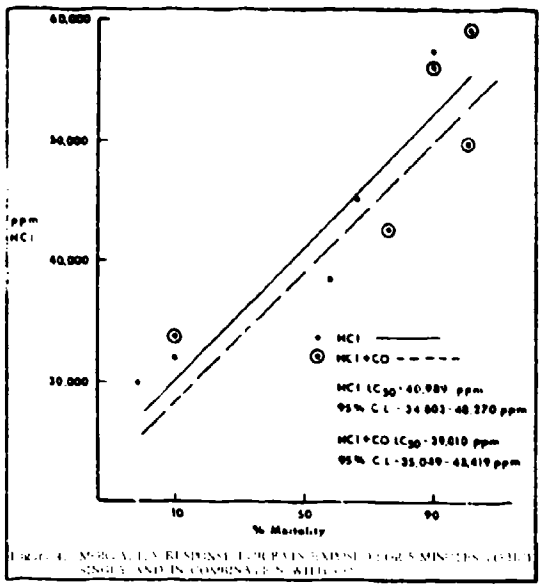
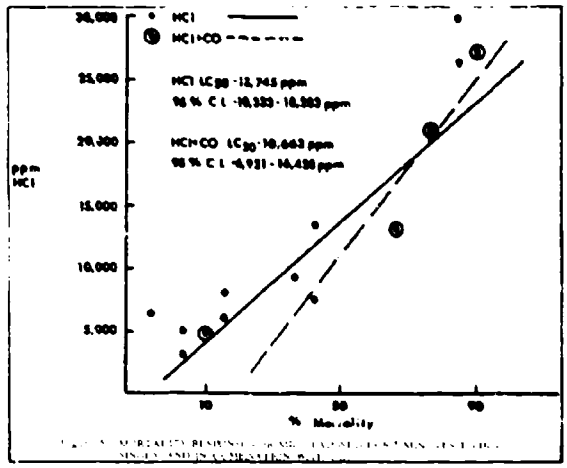


Figure 4 shows the mortality response of rats for five-minute exposures to HCl vapors and the HCl-CO combination. Once again, there is no statistically significant difference between the LC_{50} determinations of the two tests. It can be seen that the five-minute HCl vapor LC_{50} for rats is 40,989 ppm, while for the HCl-CO combination the LC_{50} is 39, 010 ppm.

Figure 5 shows the mortality response of mice for five-minute exposures to HCl and the HCl-CO combination. The mouse LC_{50} for HCl alone was determined to be 13,745 ppm. The joint exposures with CO produced an LC_{50} of 10,633 ppm. Once again, there is no statistically significant difference between these two values.





Pathology

Gross pathology findings from both HF and HCl exposures included pulmonary edema of varying degrees of severity in both rats and mice. In animals that died during or shortly postexposure, pulmonary hemorrhage was a common finding.

NITROGEN DIOXIDE RESULTS

Symptomatology

Severe respiratory distress was the only toxic sign noted during five-minute rat and mouse exposures to lethal concentrations of NO_2 and the NO_2-CO combination. Most animal deaths were seen within 24 hours postexposure with any remainder dead by 48 hours postexposure. Again, as with HCl and HF, we saw no alteration in the time-to-death pattern due to the presence of the 25% COHb levels.

Mortality Response

Figure 6 shows the five-minute rat mortality response to various concentrations of NO_2 and the NO_2-CO combination. Although there appears to be a difference in the two LC_{50} values, this difference is not statistically significant at the 95% confidence levels. Here we found the LC_{50} for NO_2 vapors to be 831 ppm and for the NO_2-CO combination, 1,140 ppm. This NO_2 LC_{50} is in good agreement with that of 833 ppm as found by another investigator (Gray et al., 1954).

Figure 7 shows the mouse response for the five-minute NO_2 and NO_2-CO exposures. Here again, there is no significant difference between the two LC_{50}'s. For NO_2 singly this value is 1,880 ppm, and for NO_2 in combination with CO the LC_{50} is 1,644 ppm.

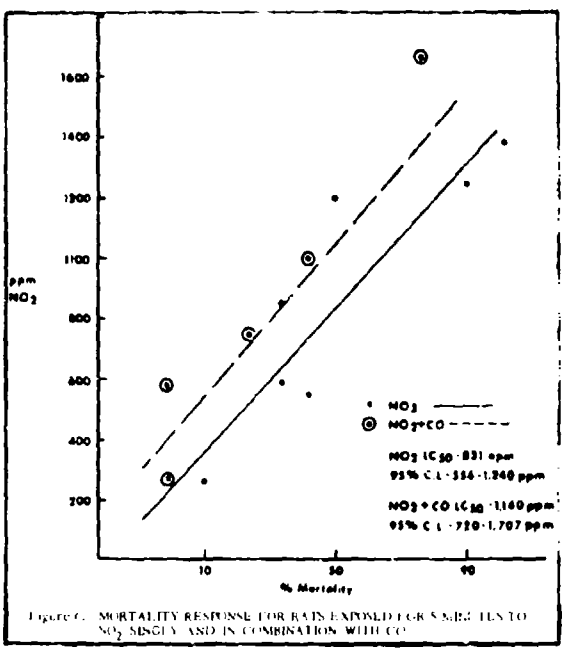


Figure 6. MORTALITY RESPONSE FOR RATS EXPOSED FOR 5 MINUTES TO NO_2 SINGLY AND IN COMBINATION WITH CO

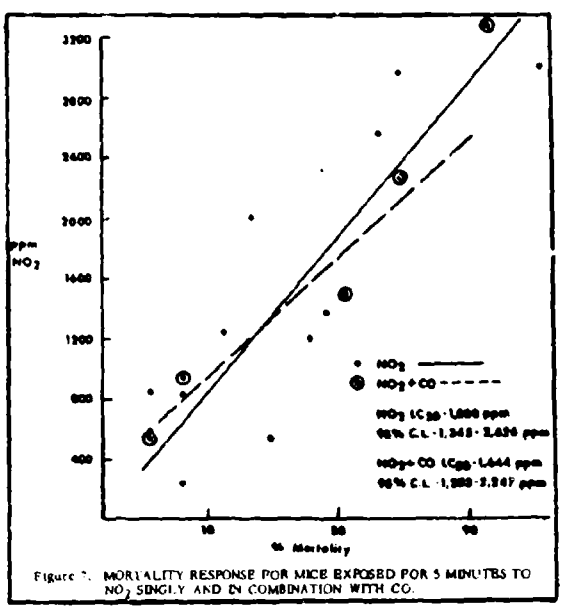


Figure 7. MORTALITY RESPONSE FOR MICE EXPOSED FOR 5 MINUTES TO NO_2 SINGLY AND IN COMBINATION WITH CO

Pathology

Gross pathology indicated that NO_2 induced animal deaths resulted from pulmonary edema with a few animals exhibiting pulmonary hemorrhage.

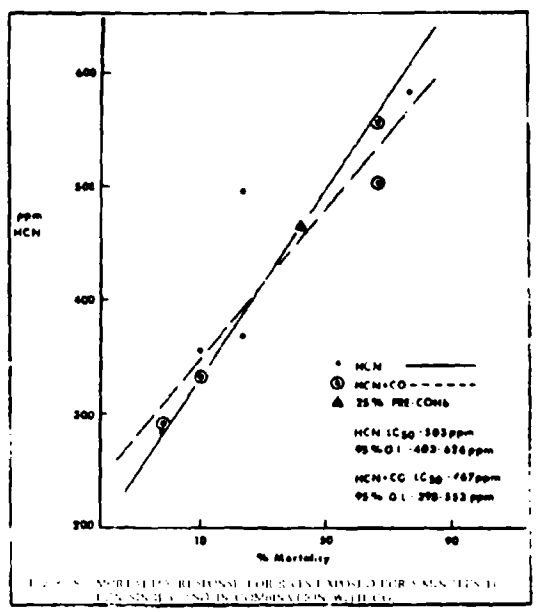
HYDROGEN CYANIDE RESULTS

Symptomatology

With regard to toxic signs, hyperactivity and asphyxial convulsions were common to both species of rodents tested. All deaths from HCN, singly or in combination with CO, occurred either during the exposure or within 20 minutes postexposure. Again, there was no alteration in the time-to-death pattern due to the presence of CO.

Mortality Response

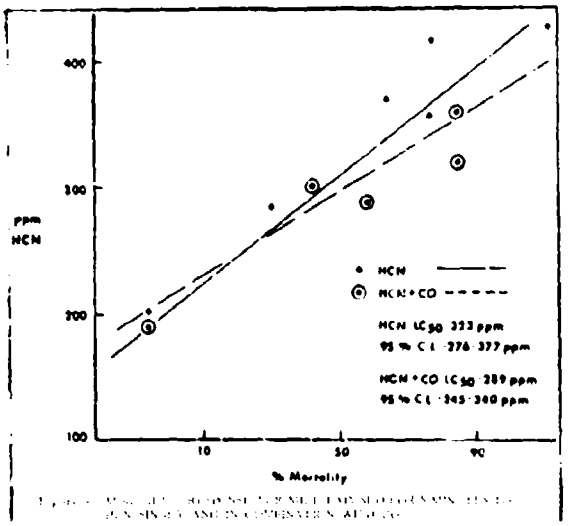
Figure 8 illustrates the five-minute rat mortality response to various concentrations of HCN vapors singly and in combination with CO. The LC_{50} for HCN was found to be 503 ppm while the HCN-CO combination produced an LC_{50} value of 467 ppm. Again, there is no significant difference in the two LC_{50} values.



We know that the primary effect of HCN intoxication is the blocking of intracellular oxygen transport through the cytochrome system, specifically through the action of the cyanide ion reacting readily with the trivalent ferric ion of cytochrome oxidase, resulting in inhibition of cellular respiration. Based on the proximity of

the rat LC_{50} values for HCN singly and in combination with CO, it did not appear that the slightly decreased extracellular oxygen transport, due to the 25% COHb level, had any effect in potentiating the toxicity of HCN. We were concerned, however, that a response might not have been seen because of the short fraction of the five-minute exposure that the animals were at the 25% COHb level. Remember, these animals had achieved 25% COHb levels only after five minutes of exposure; they did not have these levels before exposure to the various materials. To resolve this question, we exposed an additional group of rats to HCN alone, immediately following a CO exposure resulting in 25% COHb. The mortality response from this exposure is also shown in figure 8 and is represented by the triangle. It can be seen that the results of this exposure are no different from those in which the HCN and CO were administered simultaneously.

Figure 9 shows the five-minute mortality response of mice to HCN and the HCN-CO combination; and again there is no significant difference between the two LC_{50} values. The five-minute mouse LC_{50} for HCN alone was shown to be 323 ppm and in combination with CO, 289 ppm.



Pathology

Gross pathological findings from exposure to HCN showed widespread pulmonary hemorrhage accompanied by hepatic and renal congestion.

SUMMARY

Table I is a summary of the five-minute LC_{50} results for rats, ranking the four compounds tested from top to bottom in order of decreasing toxicity. The LC_{50} values are shown for each compound, with the value in parentheses being the LC_{50} for concurrent exposure with CO. Also listed are the 95% confidence limits with the values for joint exposure to CO being in parentheses. It can be seen that HCN is the most toxic to the rats, followed by NO_2, HF, and HCl.

TABLE I

FIVE-MINUTE LC_{50} RESPONSE FOR RATS EXPOSED TO HCN, NO_2, HF, AND HCl SINGLY AND IN COMBINATION WITH CO (25% COHb)

COMPOUND	LC_{50} CONCENTRATION (ppm)	95% CONFIDENCE LIMITS (ppm)
HCN (+CO)	503 (467)	403- 626 (395- 553)
NO_2 (+CO)	831 (1,140)	556- 1,240 (720- 1,707)
HF (+CO)	18,200 (18,208)	15,965-20,748 (13,698-24,202)
HCl (+CO)	40,989 (39,010)	34,803-48,270 (35,049-43,419)

( ) = Material + CO

Table II shows the same information for the mouse exposures. Again, the compounds are listed in order of decreasing toxicity, with LC_{50} and 95% confidence limits included for both single and joint exposure with CO. Once again, HCN is the most toxic, followed by NO_2, HF, and then HCl. Notice that for all the compounds tested, except NO_2, the mouse was more sensitive than the rat. For NO_2, however, the rat was more susceptible than the mouse.

TABLE II

FIVE-MINUTE LC_{50} RESPONSE FOR MICE EXPOSED TO HCN, NO_2, HF, AND HCl SINGLY AND IN COMBINATION WITH CO (25% COHb)

COMPOUND	LC_{50} CONCENTRATION (ppm)	95% CONFIDENCE LIMITS (ppm)
HCN (+CO)	323 (289)	276- 377 (245- 340)
NO_2 (+CO)	1,880 (1,644)	1,345- 2,626 (1,203- 2,247)
HF (+CO)	6,274 (6,670)	4,789- 8,149 (5,690- 7,807)
HCl (+CO)	13,745 (10,663)	10,333-18,283 (6,921-16,428)

( ) = Material + CO

CONCLUSION

As a result of these experiments, it has been shown that in terms of giving a hazard rating to various aircraft cabin materials, it must first be experimentally determined what the pyro-decomposition products are and, secondly, what their relative amounts are per unit mass of the specific material in question. For example, 100 pounds of a plastic which upon combustion yields a cabin concentration of 50,000 ppm HCl vapor would present a greater hazard than the combustion of 100 pounds of a plastic which would produce an aircraft cabin concentration of 200 ppm HCN.

These experiments also indicate that CO concentrations which are not hazardous to life do not enhance the toxicity of the four compounds as tested. In addition, the times to death for animals from both the singly exposed and the CO joint action exposures were comparable. This precludes the possibility that, although not resulting in greater mortalities at a given concentration, the addition of CO increases the hazard by decreasing the time to death.

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DISCUSSION

MR. WANDS (National Academy of Sciences): Did you observe in your animals any excessive amount of preening, either during the exposure, immediately after, or during the observation period?

MR. DI PASQUALE (SysteMed Corporation): Yes, we did. This was a common occurrence in both the nydrogen chloride and hydrogen fluoride experiments. Previous to this, we have done experiments with these compounds, and we're doing experiments now, and we are noticing the excessive preening.

MR. WANDS: You, of course, will be getting a significant ingestion of fluoride ion?

MR. DI PASQUALE: I would imagine so - also chloride.

LT. COL. STEINBERG (Edgewood Arsenal): One question on the HF - did you note any excessive loss of HF to the delivery system prior to entry into the chamber?

MR. DI PASQUALE: We did some preliminary exposures before we started this work, and the entire system was well passivated by the time we did the LC_{50}'s. For each individual exposure we did not notice much of a loss. The entire system was prepassivated with the gases before we started the series of exposures. I don't know if that answers your question. We usually found that with many of the compounds we tested when we started out with a new system, we did lose considerable amounts of the compound to passivation of the system.

DR. MC NAMARA (Edgewood Arsenal): Although there was no statistical difference when you compared carbon monoxide alone and carbon monoxide plus any of the other four compounds, in all four cases it seemed that the combination had a lower LC_{50} than the agent alone.

MR. DI PASQUALE: That is true in all cases but the nitrogen dioxide in the rat where we saw a reversal of this. It looked as though, if we can say there was a difference (which according to the confidence limits we saw there wasn't), the carbon monox e actually protected the rat. There is a reversal of what you're referring to, with nitrogen dioxide in the rat.